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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,323	06/10/2002	Steven C. Ghivizzani	18484-002320US	7834

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,323	GHIVIZZANI ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 14-32* is/are rejected.

7)☒ Claim(s) *12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 are pending in the instant application.

Specification

The disclosure is objected to because of the following informalities:

An application claiming the benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation-in-part" of the provisional application since an application that claims benefit of a provisional application is a nonprovisional application of a provisional application, not a continuation, division, or continuation-in-part of the provisional application. Appropriate correction is required.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 5 contains parts A and B. Because the figure legend does not specifically describe panels A and B, it is not clear which panel depicts the results for transforming growth factor β1 or insulin-like growth factor 1. Further, the drawings are objected to because the x-axis labels of the graphs of Figures 3A-C and 5A-B are illegible and will not reproduce well.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing

should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In addition to Replacement Sheets containing the corrected drawing figure(s), applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Marked-up Drawings" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Claim Objections

Claims 9 and 10 are objected to because of the following informalities: the claims recite the abbreviations TGF-β and IGF-1, respectively. The abbreviation should be spelled out in the first appearance of the claims and should be followed by the abbreviation in parentheses.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 provides for the use of collagen and a polynucleotide encoding a protein of interest, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 32 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 20 and 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is vague and indefinite in that the metes and bounds of the phrase "wherein said medicament is used to localize said polynucleotide to a subchondral perforation within said joint" are unclear. The phrase is unclear in that it does not appear to indicate structural characteristics that render the compound of claim 19 suitable for use in localizing said

polynucleotide to a subchondral perforation. It would be remedial to amend the claim language to clearly indicate the structural characteristics that render the compound of claim 19 suitable for the intended use. Alternatively, the intended use language can be deleted from the claim, since the phrase does not impose structural limitations on the composition of claim 19.

Claim 25 is vague and indefinite in that the metes and bounds of the phrase "wherein the medicament is delivered to a perforation within said joint and results in expression of said polynucleotide in said subchondral cells" are unclear. The phrase is unclear in that it suggests specific structural characteristics are required for the delivery of the composition and expression of the polynucleotide. However, the phrase does not clearly set forth those structural characteristics. Therefore, it is unclear as to what compositions necessarily meet the claim limitations. It would be remedial to amend the claim language to clearly indicate the structural characteristics that render the compound of claim 25 suitable for the intended use. Alternatively, the intended use language can be deleted from the claim, since the phrase does not impose structural limitations on the composition of claim 25.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing a marker gene into a perforation in a subchondral bone of a joint, whereby a subchondral cell localized to the perforation internalizes the polynucleotide and expresses the marker protein, does not reasonably provide enablement for

the use of other types of polynucleotides, such as those encoding chondrogenic proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention and breadth of the claims: The rejected claims are drawn to a method of introducing a polynucleotide encoding a heterologous protein into a perforation in a subchondral bone of a joint, whereby a subchondral cell localized to the perforation internalizes the polynucleotide and expresses the heterologous protein. The nature of the invention is complex in that gene therapy requires the construction of a vector that is capable of delivering the gene to a sufficient number of cells and directing the expression of the heterologous sequence at a sufficient level and duration to achieve a therapeutic effect. The complexity of the invention is exacerbated by the breadth of the claims. Claims 1-6 and 14-16 are very broad in that they encompass the use of any heterologous protein. Claims 7, 8, 11 and 17 are broad in scope in that they encompass the use of any heterologous protein capable of treating a cartilage defect. Claims 9, 10 and 18 are narrower in scope in that they recite the use of TGF-β and IGF-1. Regarding the vector, claims 1-11, 17 and 18 are very broad in that they encompass the use of any vector.

State of the art: An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature, Vol. 389, pages 239-242, 1997; e.g. page 239, paragraph 1) and Palù et al (J. Biotechnol. Vol. 68, pages 1-13, 1999; e.g. Abstract) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicate that most approaches suffer from poor efficiency and transient expression of the gene (e.g. page 239, right column, paragraph 2). Likewise, Luo et al (Nature Biotechnology, Vol. 18, pages 33-37, 2000) indicate that non-viral synthetic delivery systems are very inefficient (e.g. Abstract; page 33, left column, paragraphs 1 and 2). Regarding viral methods for gene delivery *in vivo*, Verma et al, indicate that lentiviral, adenoviral and AAV vectors are capable of delivery genes, but there is a possibility for insertional mutagenesis or toxicity due to an inflammatory response (e.g. Table 2). While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique (e.g. Verma et al, page 242, middle and right columns; Palù et al, pages 10-11; Luo et al, page 33, left column, paragraph 1).

Predictability of the art: The area of the invention is unpredictable. As discussed above, the method of *in vivo* gene therapy is highly complex and unpredictable. Indeed, the recent gene therapy protocols have demonstrated unpredictable outcomes resulting from an unexpected inflammatory reaction to an adenoviral vector in a patient and the insertional mutagenesis of a

gene resulting in a leukemia-like condition in children being treated for severe combined immunodeficiency (Edelstein et al, J. Gene Med. Vol. 6, pages 597-602, 2004; e.g. page 599, The hopes and the setbacks).

Further, the area of the invention regarding *in vivo* gene delivery to cells such as chondrocytes to increase cartilage deposition is unpredictable. For example, Mi et al (Arthritis Research and Therapy, Vol. 5, No. 3, pages R132-R139, 2003) disclose adenovirus-mediated intra-articular gene transfer of TGF-β1 to naïve and arthritic rabbit knee joints (e.g. Abstract; page R133, right column, paragraph 4). Unexpectedly, the expression of TGF-β1 conferred adverse effects by stimulating cartilage degradation through an unknown mechanism and resulted in a reduction in joint movement and swelling of adjacent muscles with the highest dose of the virus (e.g. page R138, paragraph bridging columns; page R134, right column, paragraph 4; Figure 2). In contrast, Mi et al note that transfer of insulin-like growth factor-1 (IGF-1) resulted in an increase in new matrix synthesis without adverse effects (e.g. page R138, paragraph bridging columns). However, Gelse et al (Current Gene Therapy, Vol. 3, No. 4, pages 305-317, 2003) caution that the apparent absence of negative side effects of IGF-1 could have been a consequence of a reduced biological potency of the transferred human IGF-1 in the rabbit rat and mouse models (e.g. page 312, right column, paragraph 2). Further, the effect of expressing molecules such as IGF-1, TGF-β and BMP-2 is unpredictable. Goldring (Expert Opin. Ther. Vol. 1, No. 5, pages 817-829, 2001) noted that further development will be required to demonstrate the clinical applicability of these molecules because IGF-1 responsiveness is decreased in chondrocytes of osteoarthritis patients, and TGF-β may induce osteophyte formation (e.g. page 824, paragraph bridging columns). Moreover, Gelse et al note that

although short-term stimuli might be sufficient for the induction of chondrogenesis, more prolonged stimulatory effects would be desired to maintain the matrix integrity to treat diseases with chronically disturbed cartilage metabolism (e.g. page 312, right column, paragraph 3).

Guidance of the specification and existence of working examples: The present specification provides little or no guidance to support the claimed invention for therapeutic gene therapy applications. The specification discloses the effects of specific therapeutic molecules *in vitro* (e.g. Example 2) but does not provide guidance to support the treatment of diseases to which the claimed process can be applied. The specification and working examples disclose a method of administering a polynucleotide to a subchondral cell by perforating the subchondral bone, thus overcoming the difficulty of administering a polynucleotide to a subchondral cell through a dense extracellular matrix. Though Applicants overcome the difficulty in administering genes to subchondral cells, there is no direction provided as to how to overcome other obstacles to gene therapy recognized by leaders in the field, e.g. transient gene expression. Therefore, there is no support for therapeutic administration of a gene such that the gene product is produced in sufficient quantity and duration to ameliorate any disease sign or symptom without side effects that contribute to the pathology of the disease.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect heterologous expression of a protein would have on a subchondral cell, whether the effect could be exploited for treatment of a disease, and how to get sufficient expression to induce at least

some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed invention. Therefore, the claimed invention of introducing a polynucleotide into a subchondral cell is not considered to be fully enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19, 20, 22, 23, 25-29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bonadio et al (US Patent No. 5,942,496; see the entire reference).

Bonadio et al teach a composition comprising one or more genes in a collagen matrix (e.g. column 5, lines 50-55; column 9; lines 16-45; column 12, lines 32-62). Further, Bonadio et al teach that the gene may be in the form of a recombinant vector that is sufficient to result in uptake and expression of the DNA (e.g. column 5, lines 50-67). Regarding the polynucleotide,

Bonadio et al teach the use of genes such as TGF-β (i.e. a cytokine that acts as a chondroprogenitor growth factor), IGF and FGF (e.g. column 13, lines 44-58; column 14, lines 10-20). Moreover, Bonadio et al teach the use of a pharmaceutically acceptable buffer to formulate either the DNA component, the matrix component or both components separately, into a more gelatinous form for application to the body (e.g. column 14, lines 40-51).

Claim 27 is rejected under 35 U.S.C. 102(e) as being anticipated by Shanafelt et al (US Patent No. 5,986,059).

Shanafelt et al teach a composition comprising a polynucleotide encoding IL-4, an inhibitor of IL-1 cytokine production, within a liposome for delivery to cells (e.g. column 3, lines 45-65; column 11, lines 9-21; column 14, lines 13-47). Further, Shanafelt et al teach the use of pharmaceutically acceptable carriers (e.g. column 13, lines 18-23). Thus, Shanafelt et al necessarily teach a composition comprising a cationic lipid complexed with a polynucleotide encoding a cytokine inhibitor in a pharmaceutically acceptable carrier.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shanafelt et al (US Patent No. 5,986,059; see the entire reference) in view of Popescu et al (US Patent No. 4,708,861; see the entire reference).

The teachings of Shanafelt et al are described above and applied as before.

Shanafelt et al do not teach a composition comprising collagen, cationic lipid and a polynucleotide.

Popescu et al teach liposome-gel compositions where the gel is formed from collagen (e.g. Abstract; column 7, lines 1-47). Further, Popescu et al teach the use of liposome-gel compounds to deliver a sustained release of the compound sequestered in the liposome (e.g. column 8, lines 13-26).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Shanafelt et al to include the liposome-collagen matrix taught by Popescu et al because Shanafelt et al teach it is within the ordinary skill in the art to use liposomes to deliver DNA encoding an interleukin inhibitor to cells and Popescu et al teach the use of liposome-gel compositions.

One would have been motivated to make such a modification in order to receive the expected benefit of sustained release of the compound (i.e. polynucleotide) as taught by Popescu et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Claims 1-11 and 14-32 are rejected.

Claims 12 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC)

for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jennifer Dunston
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jad

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PRIMARY EXAMINER